Tetrahedron 65 (2009) 7240–7248

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Guests of differing polarities provide insight into structural requirements for templates of water-soluble nano-capsules

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ARTICLE INFO

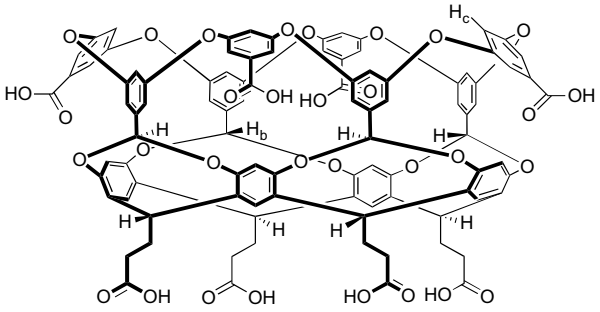
Article history:
Received 3 November 2008
Received in revised form 28 January 2009
Accepted 29 January 2009
Available online 6 February 2009

ABSTRACT

Guests covering a range of polarities were examined for their ability to bind to a water-soluble cavitand and trigger its assembly into a supramolecular capsule. Specifically the guests examined were: tridecane **2**, 1-dodecanol **3**, 2-nonyloxy ethanol (ethylene glycol monononyl ether) **4**, 2-(2-hexyloxyethoxy) ethanol (di(ethylene glycol) hexyl ether) **5**, 2-[2-(2 propoxyethoxy)ethoxy] ethanol (tri(ethylene glycol) propyl ether) **6**, and bis [2-(2-hydroxyethoxy)ethyl] ether (tetra(ethylene glycol)) **7**. In this series, guest **6** proved to signify the boundary between assembly and the formation of 2:1 complexes, and simple 1:1 complexation. Thus, guests **2**–**5** formed relatively kinetically stable capsules, guest **6** formed a capsule that was unstable relative to the NMR timescale, and guest **7** formed a simple 1:1 complex.

1. Introduction

Although common in nature, self-assemblies that are principally driven by entropy are rare among the range of synthetic assemblies reported to date.[1–3] Instead, it is routine to ensure assembly by using structural motifs that make a significant enthalpic contribution to the overall free energy change during assembly.[4–15] Recently, we have been interested in assembly systems designed to rely on entropic changes.[16,17] Specifically, we are investigating the properties of water-soluble cavitands such as **1** (Fig. 1).[18] The preorganized, bowl-shaped cavity of this host is rimmed by a ring of aromatic rings that—in the presence of a templating guest—can interface with another cavitand to form a supramolecular capsular complex (Fig. 1). We have observed that although the interface between host and host, or host and guest, only consists of enthalpically weak interactions, these capsular complexes possess a high degree of kinetic and thermodynamic stability when the entrapped guest (or guests) is relatively hydrophobic. Thus, guests as large as steroids,[19] as small as hydrocarbon gases,[20] and as flexible as *n*-alkanes all lead to stable capsules.[21] Indeed, this broad entrapment ability allows the capsule formed by **1** to function as an efficient (nanoscale) photochemical reactor.[22–28]



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It is intuitive that the stability of these capsular complexes should decrease as the hydrophobicity of the guest molecules is decreased, and this was recently demonstrated with amphiphilic aliphatic carboxylates that form stable 1:1 complexes with **1** (Fig. 1). By way of example, octanoate binds by inserting its hydrocarbon tail into the binding pocket and leaving its polar head group at the portal of the cavity. In such an orientation, the overall hydrophilicity of the (latent) dimerization interface region is increased, and the propensity of the 1:1 complex to be capped by a second cavitand reduced. In this study we examine the binding of a series of approximately isosteric guests of widely differing polarities. Our results give considerable insight into the types of molecule that can or cannot template capsule formation.

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doi:10.1016/j.tet.2009.01.106

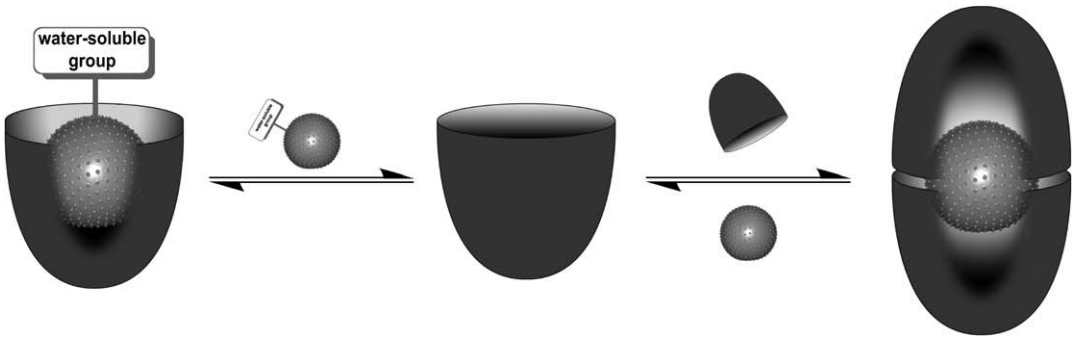

Figure 1. The assembly options to cavitand **1** (represented by the bowl). Amphiphilic guests lend themselves to 1:1 complexes, whilst more hydrophobic guests form capsular complexes (2:1 stoichiometry shown).

2. Results and discussion

2.1. The guests

We examined a number of guests of varying levels of oxygenation for their ability to bind to cavitand **1**. Specifically the guests examined were: tridecane **2**, 1-dodecanol **3**, 2-nonyloxy ethanol (ethylene glycol monononyl ether) **4**, 2-(2-hexyloxyethoxy) ethanol (di(ethylene glycol) hexyl ether) **5**, 2-[2-(2 propoxyethoxy)ethoxy] ethanol (tri(ethylene glycol) propyl ether) **6**, and bis [2-(2-hydroxyethoxy)ethyl] ether (tetra(ethylene glycol)) **7** (Fig. 2). Only two of these guests were not commercially available: 2-nonyloxy ethanol **4**, and 2-[2-(2 propoxyethoxy)ethoxy] ethanol **6**. These were synthesized by reacting ethylene glycol and triethylene glycol with 1 equiv of nonyl and propyl bromide, respectively (see Experimental section). The complex formed between **1** and tridecane **2** has been reported previously,[21] but is included here for completeness.

All 6 guests possess 13 non-hydrogen atoms, and range from 13 carbons in **2** to 8 carbons and 5 oxygen atoms in **7**. They are approximately isosteric, with a 20% reduction in volume from the largest (**2**) to the smallest (**7**), and have a range of polar surface areas ranging from zero to almost one quarter of the total area (Table 1).

2.2. 2:1 Complex formation: guest-binding region of the NMR

With the knowledge that **1** readily forms a 2:1 complex with guest **2**, we initially screened the properties of the guests by examining the ^{1}H NMR spectra arising from the addition of 0.5 equiv of guest (60 mM in DMSO) into aqueous solutions of host **1** (1 mM) and $Na_2B_4O_7$ (10 mM). The high-field (bound guest) region of these spectra (Fig. 3) is revealing. For guests **2** through **5** a range of sharp signals between ca. 1.5 and −3.2 ppm is readily apparent. COSY NMR identified these guest signals. For example, Figure 4 shows the bound guest region of the COSY NMR of the complex with dodecanol **3**. The most upfield signal at −3.3 ppm corresponds to the deeply bound C-12 methyl group, and the signals for methylenes C-11 to C-6 appear at increasingly downfield positions up to −0.1 ppm for the C-6 methylene (Fig. 4 and Table 2). This type of signal spreading is typical for alkanes within host **1**. The cavity is a pseudo, truncated cone, and so the deeper a group resides in the cavity the closer are the cavity walls and the greater the shielding. In the case of the guests here, the methyl group(s) is deeply bound and helps to fill the narrowest region of the cavity, whereas the mid-section of the guest resides in the equatorial region of the capsule and so is only shifted to ca. −0.1 ppm. Returning to the COSY NMR, the position of the signals corresponding to the C-6 to C-1 methylenes is complicated by their varying proximity to the electronegativity oxygen, but the corresponding $\Delta\delta$ values (Table 2) confirm that whilst the methyl group of **3** is binding to the narrowest region of one hemisphere, the hydroxy group is doing likewise in the opposite 'pole'. Indeed, the shifts experienced by the two penultimate groups, the C-1 and C-11 methylenes, suggest that the smaller hydroxy group binds more deeply into its hemisphere than does the methyl.

Guests **2** through **5** possess progressively shorter alkyl chains, and there is a corresponding simplification in the NMR spectrum for the region corresponding to the bound chain (0.0 to −3.2 ppm, Fig. 3). However, at the 'core' of this region, for each of these guests, the signals from the terminal pentyl group manifests itself as a common pattern of signals; the terminal methyl group the most upfield signal at ca. −3.20, the penultimate methylene at ca. −1.40 ppm, etc. This common pattern indicates that all the pentyl groups adopt similar binding motifs. Indeed, as we shall discuss (vide infra), these alkyl moieties play an important anchoring role in these complexes.

For the more oxygenated guests **4**, and **5** COSY NMR cannot assign the ethylene groups. However, assuming a packing motif similar to **2** and **3**, the signal at ca. 0.75 ppm for the complex with **4** corresponds to the more deeply bound terminal C-1 methylene, whilst the signal at ca. 1.4 ppm corresponds to its C-2 methylene neighbor (Fig. 3). For the complex with **5**, NOESY NMR demonstrated that the pairs of signals at 0.75/1.09 and 1.50/1.72 ppm corresponded to the two ethylene groups. Additionally, an NOE between the former and host atoms H_b is observed confirming that this signal pair corresponds to the terminal ethylene glycol unit.

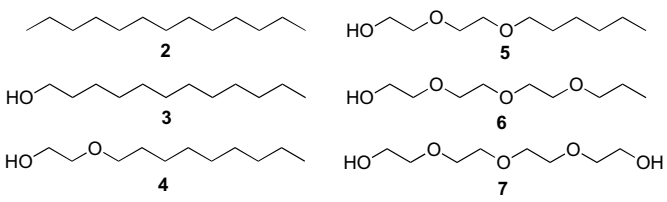

Figure 2. Guests used in this study.

Table 1
Calculated weights, areas, and volumes for guests **2**–**7**[a]

Guest	Mol. wt (g mol^{-1})	Area (Å^2)	Polar surface area (Å^2)	% Polar surface area	Volume (Å^3)
2	184.36	299.24	0	0	257.36
3	186.33	288.60	20.11	7.0	246.25
4	188.31	280.87	26.66	9.5	237.28
5	190.28	273.36	33.21	12.1	228.41
6	192.25	265.31	39.65	15.0	219.39
7	194.22	254.49	59.66	23.4	208.30

[a] Calculated using MNDO semi-empirical method on Spartan®.

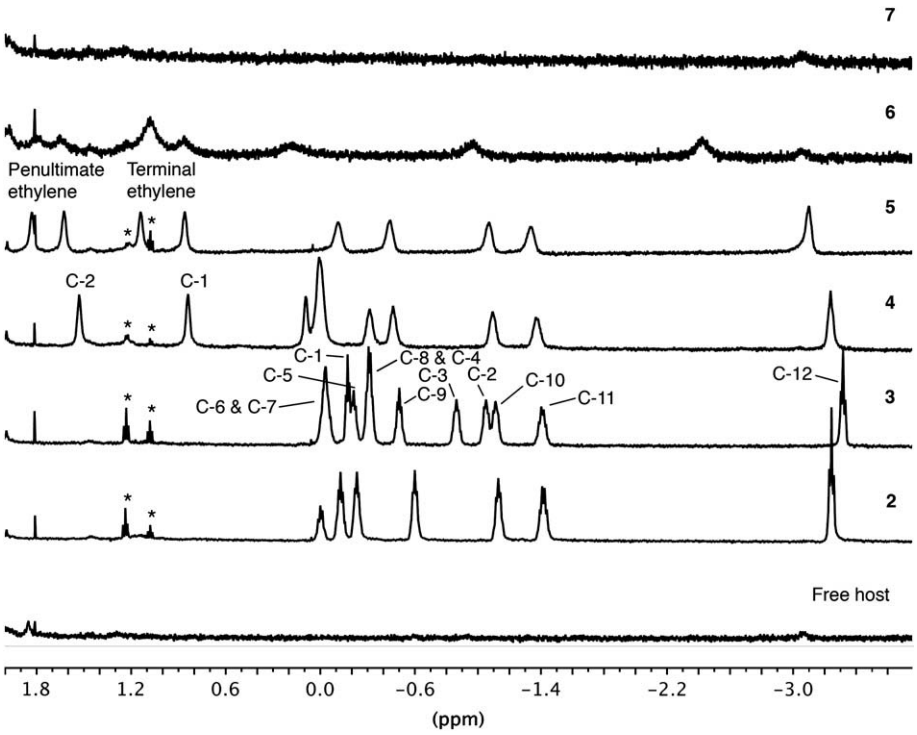

Figure 3. Guest-binding region of the NMR spectra of the complexes formed by mixing 2:1 ratios of **1** (1 mM) and guests **2**–**7** (D_2O, 10 mM $Na_2B_4O_7$). ∗ Denotes free guest.

Guests **6** and **7** differ from **2**–**5**. In the case of **6**, instead of well-defined guests signals, only broad peaks are observed (Fig. 3). This result suggests that we are dealing with faster exchanging system, but further analysis (vide infra) is required to identify whether the system is an equilibrium between free guest and a 1:1 complex, or an equilibrium between 1:1 and a 2:1 capsular complex. In the case of guest **7**, no guest peaks are observable in the guest-binding region, a fact that suggests that this guest does not bind or only weakly forms a 1:1 complex.

2.3. 2:1 Complex formation: host-binding region of the NMR

In these complexes, two sets of host protons are particularly good reporters of guest binding. Both point inward into the cavity

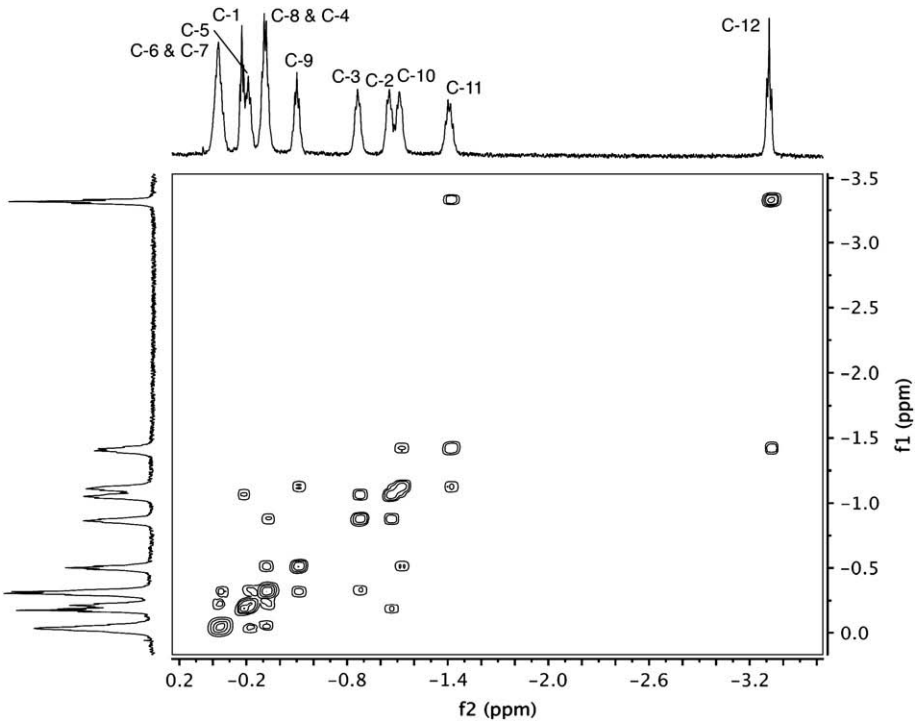

Figure 4. Guest-binding region of the COSY NMR spectrum of the complex formed between **1** and **3** (in D_2O containing 10 mM $Na_2B_4O_7$).

Table 2
NMR $\Delta\delta$ values (free in aqueous solution vs bound inside host **1**) for guest **3**

Group	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
$-\delta$	0.17	1.05	0.86	0.31	0.23	0.03	0.03	0.29	0.50	1.11	1.42	3.32
$-\Delta\delta$	3.58	2.47	2.06	1.51	1.43	1.23	1.23	1.49	1.70	2.31	2.62	4.12

(see structure **1**); the first, H_b is diagnostic of the type of guest binding within the complex, while the second set, H_c, does likewise, but being located at the dimerization interface region of the cavitand is also diagnostic of the type (1:1 or 2:1) of complex being observed. The section of the NMR spectra where the signals of these protons appear is reproduced in Figure 5.

In these complexes, 2:1 entities can be identified by integration of host and guest signals, which can be further confirmed by diffusion NMR. Complexes of 2:2 stoichiometry cannot be unequivocally identified by integration, but diffusion can differentiate between these and 1:1 complexes. Regardless, in all cases thus far, diagnostic of capsule formation is the upfield shift of the H_c signal so that it appears close to, or is obscured by, the host signal at ca. 6.50 ppm.[16,17] A comparison of the spectrum of the free host and the complexes formed by guests **2**–**5** confirm that these form 2:1 capsular complexes. In the case of the guest **6**, although the H_c peak is shifted upfield it is broadened significantly. This evidence strongly supports the notion that this guest forms a mixture of 1:1 and 2:1 complexes, or put alternatively, guest **6** forms a kinetically unstable 2:1 capsular complex of limited thermodynamic stability. In contrast, the H_c signal for the complex with guest **7** is not shifted significantly upfield and is relatively well defined. This confirms that this guest does not form a capsular complex.

The signal from H_b confirms guest complexation and gives an indication of guest mobility within the capsular complexes. For guest **2**, an upfield shift in the H_b signal upon capsule formation is observed. This is typical for alkane encapsulation.[18] With their lower symmetry, encapsulation of either **3**, **4** or **5** could be expected to lead to two different H_b signals: one for H_b protons associating with the hydrocarbon end of the guest, and one for the H_b protons interacting with its alcohol/ethylene glycol end. The fact that only one H_b is observed confirms that these guests can, on the NMR timescale, freely tumble within the (kinetically stable) capsule. This point illustrates that although the guest is needed for capsule formation, the bulk of the driving force for assembly comes mainly from host and guest desolvation rather than any specific interaction between host and guest; to a first approximation capsule integrity is independent of what the guest is *doing* inside. The position of H_b is informative in other ways. Of the different guests that form capsules, an increasing upfield shift of the H_b signal follows the order **2**>**5**>**4**>**3**. The upfield shift with guest **2** (δ=4.392–4.297) is typical for hydrocarbon guests. In contrast, the presence of one hydroxy group in guest **3** moves the H_b signal back downfield to a position (δ=4.393) almost identical to the free host. This is consistent with the notion that the set of H_b atoms—which are electron deficient benzal hydrogens—can hydrogen bond with the deeply bound oxygen atom on the guest. However, the presence of more oxygen atoms in the guest reduces the kinetic stability of the capsule and the relative strength of this hydrogen bond is reduced. Consequently, because these signals represent weighed averages of the capsular complex and free host, in the series **3**, **4**, and **5** there is a gradual upfield shift (δ=4.393, 4.354, 4.337) of the H_b signal as the capsule becomes more prone to decapping to leave one hemisphere (host) guest free.

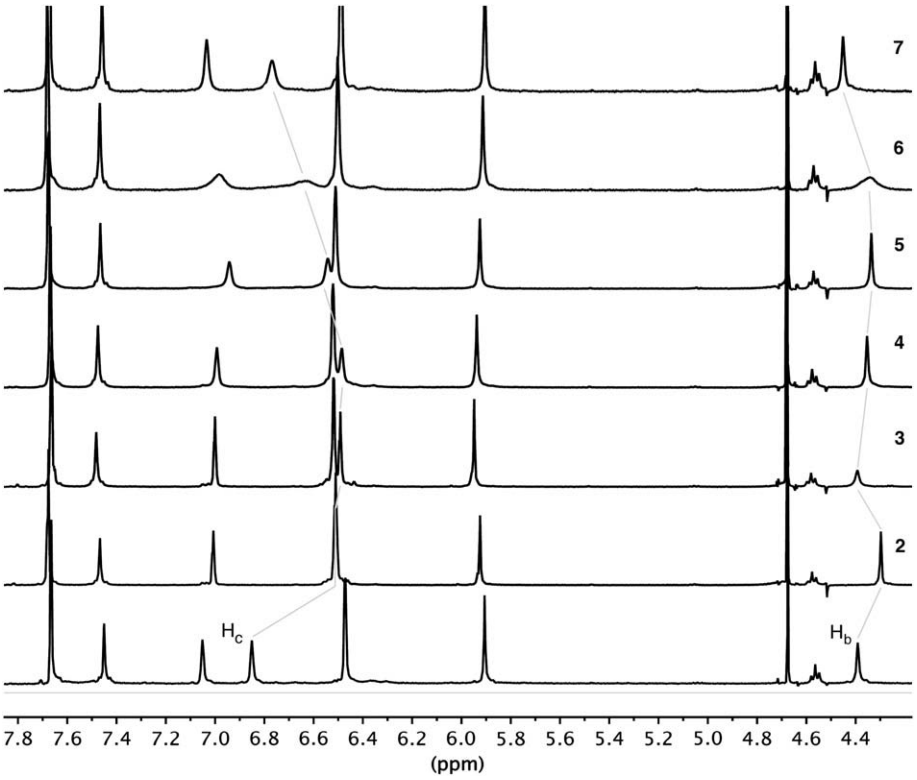

Figure 5. Host region of the NMR spectra of the complexes formed between **1** and **2**–**7** (D_2O, 10 mM $Na_2B_4O_7$).

Just as was the case with the H_c signal, the low kinetic stability of the capsule formed by **6** is also apparent in a broad H_b signal in the complex. Finally, with respect to the poorest guest, **7**, a small, but well-defined, shift is observed for the H_b signal of the host when the guest is added to the solution. This shift in the H_b signal, combined with the fact that the shift as a function of guest equivalents in a titration fits a 1:1 binding model (vide infra), confirms that tetraethylene glycol forms a weak 1:1 complex with host **1**.

2.4. NMR diffusion studies of the host–guest complexes

The aforementioned conclusions, that guests **2**–**5** form kinetically stable capsules, that guest **6** forms a capsule of low stability, and that guest **7** forms a 1:1 complex, was confirmed by Pulsed Gradient Spin Echo (PGSE) NMR experiments (Table 3). In these studies, the diffusion values (D) for free host or complex were determined from the average diffusion value obtained from three host peaks. As anticipated, the fastest (smallest) entity was the free host **1** ($D=1.84\times10^{-6}$ cm^2 s^{-1}). This corresponds to a hydrodynamic volume of 7.0 nm^3. In contrast, all of the complexes diffused more slowly than the free host. The main contributing factor to this observation is the assembly of the host. Thus, the diffusion rate of the tridecane (**2**) complex ($D=1.24\times10^{-6}$ cm^2 s^{-1}) corresponds to an entity three times the volume of the free host. This value is typical for these capsular complexes.[16,17] With increasingly polar guest the stability of the capsule decreases, the preponderance of the 1:1 complex increases, and the measured diffusion value increases. Thus, the observed hydrodynamic volumes of the complexes decrease in the series **2** through **7**. The fact that the diffusion rate of the 1:1 complex with **7** ($D=1.73\times10^{-6}$ cm^2 s^{-1}) is slower relative to the free host can be attributed to three factors. First, if the binding pocket in the empty host is collapsed to any extent, guest binding will enlarge the apparent size of the host. Second, because the guest is too large for the pocket of **1** it inevitably protrudes out into free solution and thus increases the apparent size of the complex. Third, any propensity for the 1:1 complex to cap and form a 2:1 complex may increase its apparent size. Overall there is a distinct correlation between the diffusion data and the guest polar surface area (plot not shown), but the fit is not excellent presumably because of the indirect relationship between guest structure and the 1:1/2:1 equilibrium.

2.5. Titration experiments using excess guest

The addition of 0.5 equiv of the different guests to host **1** revealed a good deal of information about their ability to trigger capsule formation. For an alternative perspective on this ability, we titrated the host with excess guest to determine if the equilibrium between the 2:1 and 1:1 complexes could be noticeable shifted in the presence of excess guest.

For both tridecane **2** and dodecanol **3**, the addition of excess guest led to no changes in the signals for the host–guest complex, confirming again that both these guests form highly stable capsular complexes. The situation was different with nonyl ether **4** (Fig. 6). At 0.75 equiv of guest, the guest signals corresponding to the capsule broaden and begin to shift, and at 1.0 equiv of guest its signals are almost broadened into the baseline. At 1.75 equiv new guest peaks can be seen to build in, and these continue to shift and change shape up to the point that almost 5 equiv of guest are added. The presence of new guest peaks when excess guest is added strongly suggest that a 1:1 complex is being formed at the expense of the 2:1 capsule, and indeed, the host signals (not shown) are typical for 1:1 complexes of this type. The significant broadening of the guest signals indicates that however much capsular complex remains in the presence of 4.75 of guest, it is in exchange with the 1:1 complex at a rate close to the NMR timescale. This observation can be rationalized in terms of how best to solubilize excess guest. Thus, the ethylene glycol tail of **4** is sufficiently water soluble that it is thermodynamically more favorable to form 1:1 complex at the expense of capsule; better to bind all of the nonyl chains leaving some ethylene glycol moiety dangling in free solution than to completely envelop as much guest as possible and leave some guest fully exposed to solvent.

A similar trend is observed with the hexyl ether guest **5**, but in this case, the capsular complex persisted to higher equivalents of guest. In other words, the free energy difference between the 1:1 and 2:1 capsules is greater with guest **5** than with **4**. What is at the root of this increased free energy difference? Is the 2:1 complex with **5** stronger relative to guest **4**? Or is the 1:1 complex with guest **5** weaker than the corresponding complex with **4**? It is hard to conceive that the hexyl anchor of **5** binds more strongly than the nonyl anchor of **4**, but readily conceivable that **5** forms a weaker 1:1 complex. Hence, we attribute the greater persistence of capsule in the case of guest **5** to a weaker 1:1 complex relative to the 2:1 capsular species.

The initial analysis of the properties of **6** pointed toward a relatively poor guest that formed a kinetically unstable capsule. The addition of excess **6** to a solution of host **1** confirmed this. Thus, even a slight excess of this guest led to new peaks of a 1:1 complex building in, and at 1.75 equiv the sample contained essentially only 1:1 complex. In contrast to the other guests, **7** led to the most straightforward of systems with no evidence of 2:1 capsular complex. With only free host and guest or 1:1 complex present at any time during the titration experiment, it was possible to fit the smooth shift in the signal from H_b of the host to a 1:1 complexation model. The measured association constant from this titration of the 'weakest' of binding guests was 2500 M^{-1} ($\Delta G^\circ=-4.6$ kcal mol^{-1}).

2.6. Variable temperature NMR studies on selected complexes

Guests **2** and **3** strongly favor capsule formation, whilst **7** forms only 1:1 complex. To gain more insight into the intermediate guests **4**–**6**, we carried out variable temperature analysis of a mixture of **1** in the presence of excess (4.75 equiv) **4**. The guest region of the NMR spectrum of this mixture in Figure 6 is reproduced in Figure 7 alongside the spectra at elevated temperatures and that of the free

Table 3
Diffusion rates (determined by PGSE–NMR) and guest polar surface area for the complexes formed between host **1** and guests **2**–**7**

Entity	Diffusion rate ($\times10^{-6}$ cm^2 s^{-1})	Calculated hydrodynamic radii (nm)[a]	Calculated hydrodynamic volume (nm^3)	Guest polar surface area (Å^2)
Free host **1**	1.84	1.2	7.0	—
Complex with **2**	1.24	1.8	22.8	0
Complex with **3**	1.36	1.6	17.3	20.11
Complex with **4**	1.37	1.6	16.9	26.66
Complex with **5**	1.41	1.5	15.5	33.21
Complex with **6**	1.55	1.4	11.7	39.65
Complex with **7**	1.73	1.3	8.4	59.66

[a] Calculated from the Stokes–Einstein equation assuming a spherical entity ($D=k_bT/(6\pi\eta r_s)$).

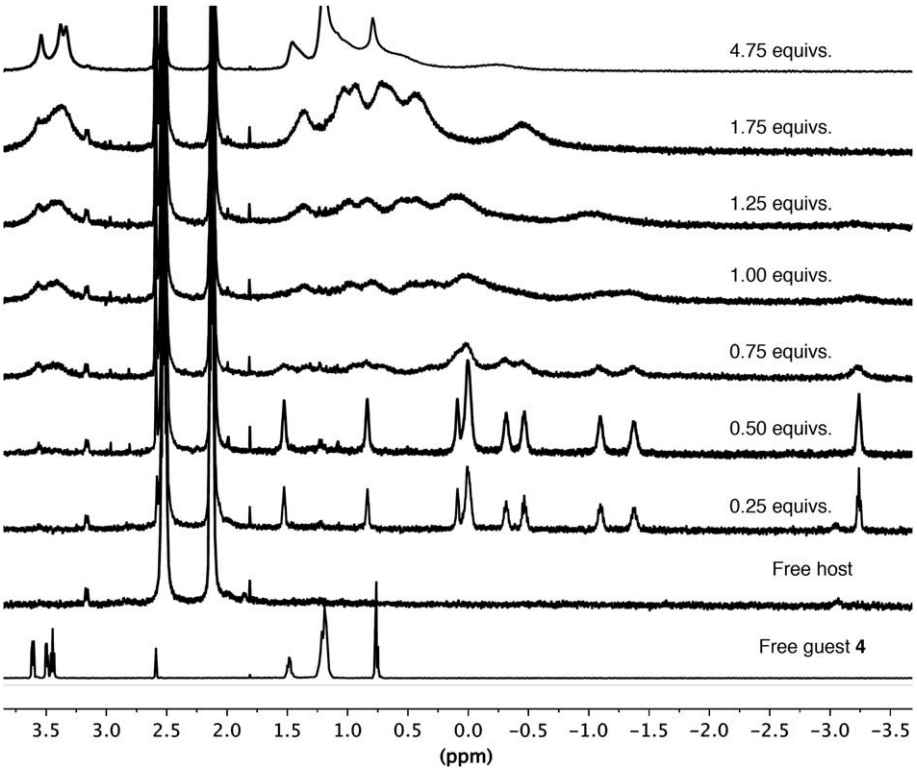

Figure 6. Guest region of the NMR spectra of the complexes formed between **1** and **4** during a titration of an excess of the latter to host **1** (in D_2O containing 10 mM $Na_2B_4O_7$).

guest. The titration experiment outlined in Figure 6 demonstrated that the presence of excess guest **4** leads primarily to a 1:1 complex; a species that is in exchange on the NMR timescale with a kinetically unstable capsule. As depicted in Figure 7, as the temperature of the system with excess guest is raised, it moves toward a regime that is exchanging slowly on the NMR timescale. Thus, the guest peaks are sharpened as the temperature is increased, and begin to decoalescence at 75 °C. A comparison with

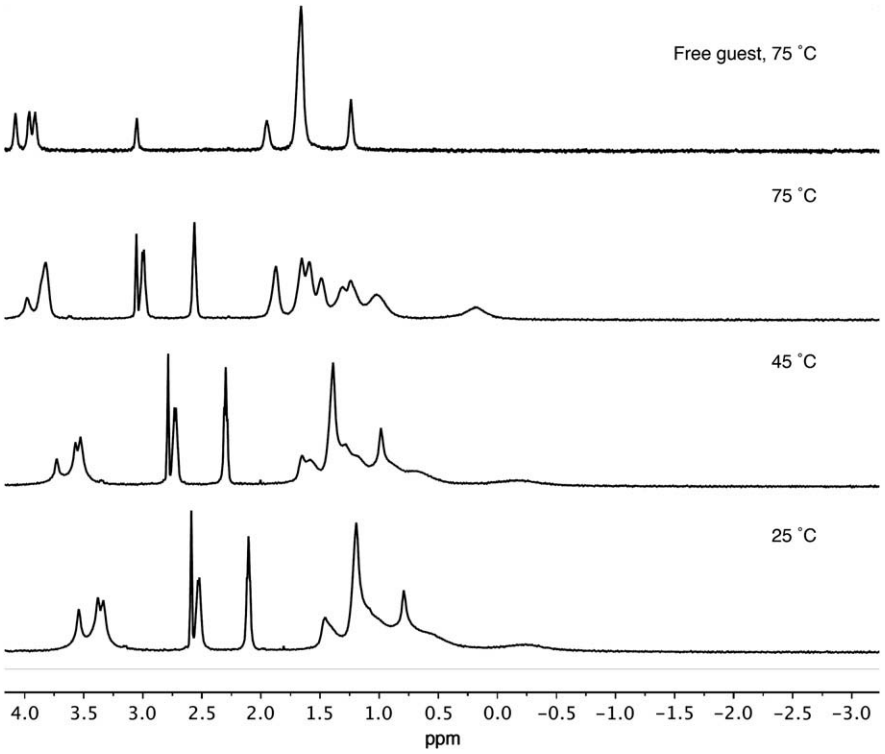

Figure 7. Variable temperature NMR analysis of the complexes formed between **1** (1 mM) and **4** (4.75 mM) in D_2O containing 10 mM $Na_2B_4O_7$.

the NMR spectrum of the free guest at the same temperature reveals that raising the temperature brings the system toward slow exchange with free **4**. We interpret these results as an increasing difference between the stability of the 1:1 and 2:1 complexes. As the temperature is increased, either the 1:1 complex is becoming more stable, the 2:1 complex less so, or both. Whichever is true, as the temperature is increased the amount of 2:1 complex decreases and the fast exchanging between it and the 1:1 complex is shut down. Presumably this shuts down entirely at even higher temperatures, but whether this occurs before the equilibrium between the free guest and the 1:1 complex itself becomes fast on the NMR timescale could not be determined because of the temperature limitations of the probe.

2.7. Competition experiments between guests

The aforementioned experiments revealed the propensity of guests **2**–**7** to form capsular complex. We next attempted to quantify these assemblies. Unfortunately, for guests **2**–**5**, binding was too strong to determine association constants by NMR. However, the fact that no (i.e., <5%) free guest was observed in a mixture of 0.5 mM **1** and 0.5 mM **5**, allowed a *lower* limit of K_{app} of ca. 750,000 M^{-1} to be calculated.[29] Although it was not possible to fully quantify assembly, we did seek further information by performing competition experiments in which a capsule containing a guest was titrated with the next poorest guest.

In the first experiment, tridecane (**2**) capsule was titrated with dodecanol (**3**). The addition of an equimolar amount (relative to guest **2**) of guest **3** led to a well-defined system containing the two capsular complexes in a 3:1 ratio (Fig. 8). As expected, the addition of increasing amounts of **3** led to the corresponding increase in the amount of the capsular complex with **3**. A calculation of the relative binding constant at 0.5 equiv of each guest gave K_{rel}=9. Hence, replacing the terminal OH group with a CH_3 group—a steric change of >5%—results in an almost one order of magnitude increase in binding affinity. Such a change in affinity is not normally observed with small guest volume changes. Hence, it is likely that desolvation of the free guest and C–H···π interactions between host and guest are more significant contributors to the overall affinity than the simple filling of space.

At 1 mM host concentrations, both guests **3** and **4** independently form capsular complexes. However, in competition with each other this is not the case. In the titration of guest **4** into a solution of the capsule containing **3**, the addition of 1 equiv of **4** (relative to **3**) led not to a mixture of the two capsular complexes, but to a competing mixture of the capsular complex of **3** and the 1:1 complex with **4**. This was apparent in the appearance of new signals at ca. 1 ppm typical of 1:1 complexes and the broadening of signals from the signals from the capsule. Why this happens can again be rationalized in terms of having an excess of amphiphilic guest and the thermodynamic need to bind as many hydrophobic anchors as possible. Unfortunately, because of line broadening and the presence of the multiple complexes, it was not possible to ascertain a K_{rel} for capsule formation. A similar situation was found with the other guests; competition with guest pairs **4** and **5**, **5** and **6**, and **6** and **7** led to broad signals and mixtures of free species and capsular and 1:1 complexes. Quantification was therefore not possible.

3. Conclusions

In summary, a set of guest molecules that vary in their oxygen content and hence polarity, have been studied for their propensity to form capsular complexes with host **1**. The most hydrophobic of these, tridecane **2**, forms a strong, kinetically stable capsule. Replacement of one of the terminal methyl groups with a hydroxy group (dodecanol **3**) reduces affinity by an order of magnitude. Nevertheless, this guest is still a strong capsule promoter. When an additional methylene group is replaced with an oxygen atom, i.e., ethylene glycol monononyl ether **4**, the guest also promotes capsule

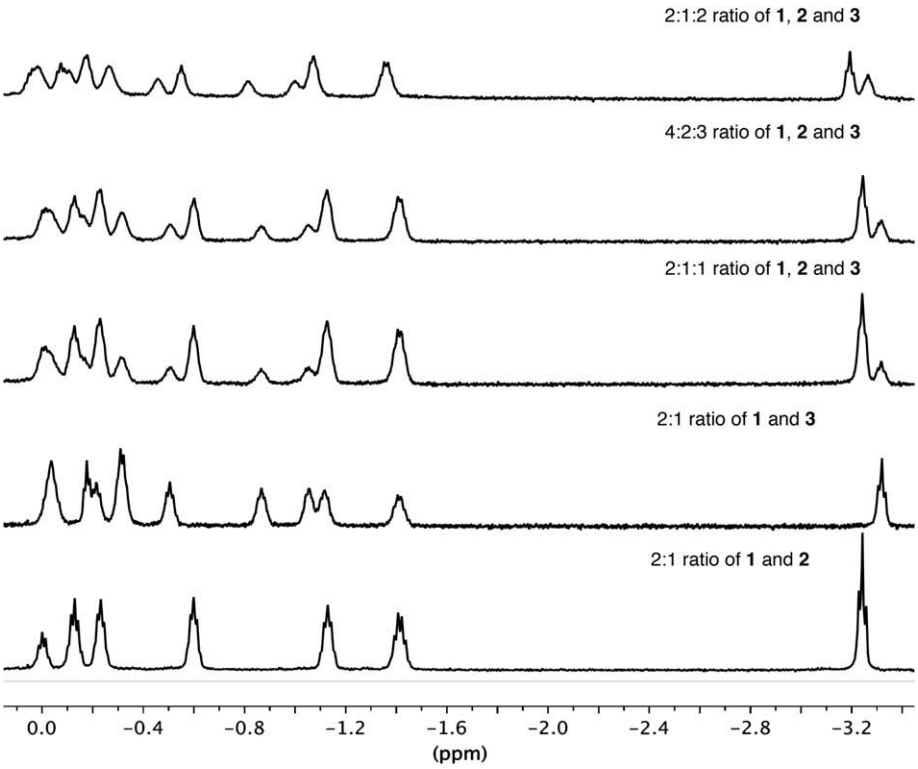

Figure 8. NMR analysis of the competition between complexes formed by tridecane (**2**) and dodecanol (**3**), and host **1** (1 mM in D_2O containing 10 mM $Na_2B_4O_7$).

formation, but only when present in up to stoichiometric amounts. Beyond a 2:1 host to guest ratio the ethylene glycol tail of this guest is sufficiently water soluble that it is thermodynamically more favorable to form 1:1 complex at the expense of capsule. This phenomenon was also observed with di(ethylene glycol) hexyl ether **5**. However, with this guest the 1:1 complex is less stable relative to the 2:1 capsular complex and more of an excess of **5** is required to break its capsular complex than was the case with guest **4**. A significant break in capsule forming propensity is seen with highly oxygenated tri(ethylene glycol) propyl ether) **6**. This guest, with nearly a 40% polar surface area, does form a capsular complex, but its kinetic stability is relatively low and exchange between 1:1 complex and 2:1 capsular complex is close to the NMR timescale. Finally, there was no evidence that the most polar guest, tetra(ethylene glycol) **7**, formed capsular complex. Nevertheless, this weakest of guests still forms a 1:1 complex with host **1**, and in doing so liberates almost 5 kcal mol^{-1} of free energy.

Although not perfect isosteres, these guests provide a valuable picture of how changes in polarity/water solubility control capsule formation. In related work, we are also looking at (isosteric) constitutional isomers that differ in where a functional group is located in the guest. These will provide further information pertaining to the assembly and complexation properties of **1**, and will be reported in due course.

4. Experimental

4.1. Materials

Tridecane **2**, dodecanol **3**, 1-bromononane, ethylene glycol, triethylene glycol, tetraethylene glycol **7**, sodium hydride, and sodium tetraborate were purchased from Aldrich. Diethylene glycol monohexyl ether **5** and 1-bromopropane were purchased from Fluka. All chemicals were used without further purification. The synthesis of host **1** has been previously reported.[19] The guests 2-nonyloxy ethanol (ethylene glycol monononyl ether) **4** and 2-[2-(2 propoxyethoxy)ethoxy] ethanol (tri(ethylene glycol) propyl ether) **6** were prepared by mono-alkylation of tri(ethylene glycol) and di(ethylene glycol), respectively. All solvents were used directly from the bottle without additional purification. Deuterated solvents were purchased from Aldrich. NMR (^{1}H) spectra were recorded on Varian Inova 500 MHz spectrometer at room temperature unless otherwise stated. Spectra processing were carried out using Mnova software (Mestrelab Research S.L). Chemical shifts are reported in parts per million (ppm) relative to H_2O as internal reference.

4.2. NMR studies

Titration studies were carried on a 0.6 mL sample of a 1 mM solution of host **1** in D_2O containing 10 mM sodium tetraborate. The guests were dissolved in DMSO-d_6 to give a 60 mM solution. Aliquots of 2.5 μL of each guest solution were added to host solution and the NMR recorded. Diffusion experiments were carried on according to a previously published procedure.[20] Binding constant determinations was performed by fitting the binding isotherm with Origin.[30] The reported value is the average of two values.

4.3. Synthesis of 2-nonyloxy ethanol (ethylene glycol monononyl ether) 4[31]

To a 50 mL round bottom flask was added, 5 mL of THF, 0.206 g (3.3 mmol) of ethylene glycol and 3.3 mmol of 1-bromononane. To this solution was slowly added a pentane washed suspension of 3.6 mmol NaH in 5 mL THF. The reaction was stirred at 60 °C for 3 days. The reaction was allowed to cool down to rt before quenching with methanol. The solvent was removed under reduced pressure and the product extracted twice with $CHCl_3$ from water. The product (an oil) was isolated by column chromatography ($CHCl_3$ mobile phase) in 16% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78–3.68 (m, 2H), 3.54 (m, 6.2, 2H), 3.47 (t, J=6.7 Hz, 2H), 1.97 (t, J=6.1 Hz, 1H), 1.27 (m, 14H), 0.88 (t, J=6.9 Hz, 3H); MS (ES): calcd [M+Na^+] 211; found [M+Na^+] 211.3.

4.4. Synthesis of 2-[2-(2 propoxyethoxy)ethoxy] ethanol (tri(ethylene glycol) propyl ether) 6[32]

To a 50 mL round bottom flask was added, 5 mL of THF, 0.5 g (3.3 mmol) of triethylene glycol, and 3.3 mmol of 1-bromopropane. To this solution was slowly added a pentane washed suspension of 3.6 mmol NaH in 5 mL THF. The reaction was stirred at 60 °C for 3 days. The reaction was allowed to cool down to room temperature before quenching with methanol. The solvent was removed under reduced pressure and the product extracted twice with $CHCl_3$ from water. The product (an oil) was isolated by column chromatography ($CHCl_3$, then 5% acetone 95% $CHCl_3$ mobile phase) with a yield of 37%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82–3.53 (m, 12H), 3.42 (t, J=6.8 Hz, 2H), 2.60 (s, 1H), 1.68–1.52 (m, 2H), 0.91 (t, J=7.4 Hz, 3H). MS (ES): calcd [M+Na^+] 215; found [M+Na^+] 215.2.

Acknowledgements

CLDG and BCG gratefully acknowledge the National Institutes of Health for financial support (GM074031).

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29. It has not been possible to measure the individual binding constants relating to the two steps of the assembly of these complexes, i.e., $H+G \rightleftharpoons HG$ and $HG+H \rightleftharpoons H_2G$. Consequently, two options are available. The first, i.e., define the association constant derived from $2H+G \rightleftharpoons H_2G$, was not chosen because with units of M^{-2} the results are hard to relate to other binding constants. Rather, the favored approach was to define the apparent association constant 'K_{app}' from the equation $H+G \rightleftharpoons HG$, where H corresponds to an empty capsule. This approach, common in biochemistry where unquantifiable equilibria 'ahead' of an equilibrium constant of interest are not considered (see: Alberty, A. *Pure Appl. Chem.* **1994**, *66*, 1641–1666), 'ignores' the fact that the host has only a limited propensity to assemble in the absence of guests. It does however give a better gauge of the strength of guest binding.
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